A NON-LINEAR REGISTRATION METHOD FOR DCE-MRI AND DCE-CT COMPARISON IN BLADDER TUMORS

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ABSTRACT

The objective of this work is to examine the feasibility of a method to register dynamic contrast enhanced computed X-ray tomography (DCE-CT) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) datasets in order to make possible the comparison of parametric maps generated from tracer kinetic modeling. First, the CT and MR dynamic sets were matched temporally using a cross-correlation maximization approach. The registration was then performed through an affine transformation followed by a non-linear registration using free-form deformations (FFDs) based on B-splines. This was determined from the CT-MR pair that maximized Normalized Mutual Information (NMI). Then the 'extended Kety' model was fitted to both CT and MR and K^{trans}, v_e and v_p parameters were obtained. The method was applied to 5 patients with bladder tumors. After registration, the overlap matching between CT and MR volume of interest (VOI) was on average 91%.

Index Terms—registration, inter-modal, DCE-MRI, DCE-CT, tracer kinetic modeling

1. INTRODUCTION

During dynamic contrast-enhanced MRI (DCE-MRI) and dynamic contrast-enhanced X-ray CT (DCE-CT), a contrast agent is introduced into the bloodstream. Dynamic image acquisition after contrast agent administration permits the differentiation of tissues on the basis of different contrast agent uptake behavior, as measured by the change in voxel signal intensity and subsequently-calculated changes in contrast agent concentration. The relationship between the contrast agent concentration change and microvascular function can be described using tracer kinetic models. By fitting a time series model to each voxel in a volume of interest (VOI) it is possible to estimate different parameters related to the microvascular status of tumors.

DCE-MRI is the method of choice for monitoring changes in tumor microvascular functional status due to antiangiogeneic and antivascular treatments [1]. However, DCE-CT is an attractive alternative as it has wider clinical availability, due to which it has attracted considerable recent interest [2]. DCE-MRI is known to have some advantages over DCE-CT – in particular, it is able to provide volume coverage at high temporal resolution without ionizing radiation. Although DCE-CT is capable of higher still temporal resolution, it is limited in the total number of slices and number of time points during the dynamic acquisitions due to dose restrictions, which means that potentially important information from spatially heterogeneous tumors may be missed. However, DCE-MRI is thought to have some accuracy limitations due to its sensitivity to variable rates of water exchange between tissue compartments [1].

A comparison between DCE-MRI and DCE-CT allows the relative limitations of the methods to be quantified. However, this comparison is not trivial as DCE-MRI and DCE-CT are acquired using different imaging systems, with different volume coverage and generally at different resolutions (both spatial and temporal). To guarantee a correct voxel by voxel comparison, the two dynamic sets should be in the same coordinate system and a correction should be performed for any deformation inside the tumor VOI. Hence CT and MR images should be co-registered.

A problem for registration, in addition to the differences in geometry and contrast, is the temporal matching of CT/MR pairs. In the dynamic data sets, image features may change over time due to the contrast agent distribution and this may affect the registration process, leading to different results depending on the CT-MR pairs used to calculate the transformation.

In this paper, we describe a novel method to compare DCE-MRI and DCE-CT parametric maps. Before performing registration, the CT-MR image series are synchronized using a method based on the cross-correlation between the gradient of the CT and MR signal intensities. Then, Normalized Mutual Information (NMI) is used as an image similarity index to choose the best CT-MR pair. Registration is based on a procedure that is composed of an affine transform to match the coordinate systems, followed by a non-linear registration inside the tumor volume of interest (VOI) to correct for tumor deformations. After these steps, DCE-MRI and DCE-CT quantitative microvascular parameters are calculated and the parametric maps compared.

2. MATERIALS AND METHOD

2.1. Experimental Protocol and Image Acquisition

Subsequent to approval by the local research ethics committee, five male patients (ages 54 to 80, mean 68.2 yrs) with a confirmed diagnosis of primary bladder tumor of types T2-T4 inclusive, were recruited. The patients underwent DCE-CT followed by DCE-MRI within a maximum time window of 1 week. The location of the

DCE-CT slices was incorporated within the 3D DCE-MRI imaging volume to allow optimal correspondence for comparative analysis.

DCE-CT was performed on a GE Lightspeed plus scanner (Milwaukee, WI, US). Scanning was carried out at 1 s temporal resolution for the first 60 s, followed by a 1 s scan every 30 s for a further 4 min (5 min total scan time). Omnipaque 300 (Amersham Health, Amersham, UK) was administered (at a fixed interval of 5 s immediately before the start of scanning) as a standard dose bolus at a rate of 5 ml/s. Images were reconstructed to a 512 × 512 × 4 matrix, slice-thickness 5 mm.

DCE-MRI was carried out on a Philips Intera 1.5 T system using a 3D T_1-weighted radiofrequency spoiled fast field echo (FFE; spoiled gradient-echo) method [3]. Native tissue T_1 was determined in order to allow contrast agent concentration calculation using acquisitions at flip angles of 2°, 10° and 30° (TR=4 ms, TE=0.8 ms and 5 signal averages). The dynamic acquisition consisted of 75 volumes (flip angle 20°, TR=4 ms; TE=0.8 ms, matrix 128 × 128 × 25, slice thickness 4 mm) at a temporal resolution of 4.97 s, generating a total scan time of approximately 6 min. The volume matrix was 128 × 128 × 25, 4 mm thickness. For contrast, 0.1 mmol/kg Omniscan (Amersham Health, Amersham, UK) was administered as a bolus using a power injector at a rate of 2 ml/s.

2.2. Temporal matching

In order to calculate the best transformations to match the DCE-MRI and DCE-CT series it is necessary to first find a correspondence between CT/MR data-sets considering contrast agent uptake events (mainly onset of enhancement) that determines variations in the image features with time. For this purpose, time series were generated of the mean signals inside the CT and MR tumor VOIs. Firstly, the two mean signal time series were resampled at the same temporal resolution (1 s). Then the cross-correlation of the gradient of the mean signal intensity time course was calculated to find the temporal delay between CT and MR. The gradient was found to be a more robust measure for this task than the mean signal value. The original CT and MR dynamic images were then synchronized using this delay (Fig.1) and all temporally matched pairs were identified.

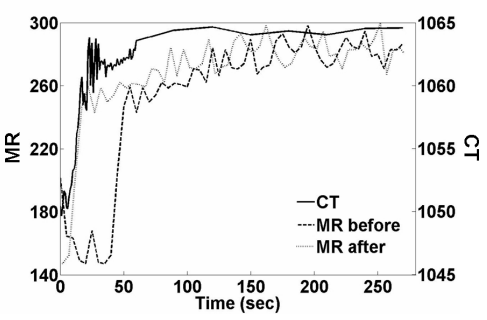

Fig. 1. MR before (dashed line) and after (dotted line) temporal alignment compared to CT (solid line) VOI mean signals.

2.3. Spatial matching

Volume registration was performed using the software developed by Rueckert [4]. This is an intensity-based method that enables one to carry out 3D non linear registration as a combination of affine transformations to match coordinate systems and cubic B-spline-based free form deformations (FFD's) to correct local shifts.
The optimal transformation is determined by minimizing a registration cost function that represents a combination of the cost associated with the smoothness of the transformation and the cost associated with the image similarity (NMI). A more extensive description of the registration algorithm can be found in [4].

Prior to registration the DCE-MRI data was up-sampled to the same resolution as the CT to ensure no loss of information from the CT data. For the CT series, the scanner bed and other objects not present in the MR images were automatically removed using morphological operators and thresholds.

We computed an affine registration of each CT and MR pair, considering the CT as the source (non-target) image. Each transformation was then applied to the whole series and the mean NMI was calculated between the CT and MR images. The affine transformation that gave the maximum mean NMI was selected as the transformation to apply to the dynamic data-set. This also indicated the image pair on which to calculate the non-linear transformation.

The obtained affine transformation was inverted and applied to the MR images and to the MR tumor VOI. This step is necessary, because transformation of CT (which has only 4 slices, as opposed to 25 in MR) could cause a loss of part of the lesion in edge slices after interpolation.

After affine registration to bring the CT and MR into the same coordinate system, a dilated bounding box surrounding each tumor VOI in the two images was defined. It was within these that the non-linear transformation was calculated. Finally, the non-linear transformation was applied to the MR volumes.

2.4. DCE-MRI and DCE-CT processing

Native T_1 in each voxel was determined from the variable flip angle baseline data by applying the standard relationship describing signal from a spoiled gradient echo acquisition at short TE [5]. T_1 at each subsequent time point was determined as in [3]. Concentration of contrast agent was then determined from the change in T_1, assuming the longitudinal relaxivity of the contrast agent to be 4.5 $s^{-1}mM^{-1}$ [6].

The arterial input function (AIF) was determined for both the DCE-MRI data and the DCE-CT data using an automated procedure similar to that described in [7].

The contrast agent concentration in DCE-CT images is linearly proportional to the change in Hounsfield units and therefore also to the change in signal intensity. Hence the raw signal data was used directly (with the baseline subtracted) in the compartmental modeling analysis.

2.5. Tracer Kinetic Modeling

The 'extended-Kety' model [8] was employed for tracer kinetic analysis:

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(t') \exp\left(\frac{-K^{trans}(t-t')}{v_e} \right) dt'$$

where C_t is the concentration of contrast agent in the observed tissue, C_p is the concentration in the blood plasma of the supplying

blood vessel (the arterial input function (AIF)), v_p the fractional blood plasma volume, K^{trans} the volume transfer constant and v_e the fractional extravascular extracellular space volume.

The model was fitted voxel-by-voxel using a non-linear least squares simplex algorithm within the tumor volumes of interest, as identified by an experienced radiographer. The maps were generated at two different resolutions: high (CT resolution) and low (MR resolution).

2.6. Evaluation method

Usually, to assess the performance of image registration, some similarity index is used (e.g. cross correlation or NMI). For intermodal registration a suitable index is NMI because it is not affected by contrast differences. However, in our case, as the registration algorithm is guided by NMI maximization, the NMI increase after registration cannot also be used for evaluation of the registration. In addition, our goal is to have the best correspondence between the CT VOI and the MR VOI. It is possible that genuine and important differences in signal or tracer kinetic model parameter maps exist after successful registration. Therefore, to assess the improvement that registration produces in the matching of CT and MR VOI, a percent overlap ratio (OR) is calculated:

$$OR\left[\%\right] = \frac{CTVOI \cap MRVOI}{CTVOI} \cdot 100$$

where $CTVOI \cap MRVOI$ is the number of matching voxels between the two VOIs, while CTVOI is the number of voxels of the CT VOI, used as reference (Fig. 2).

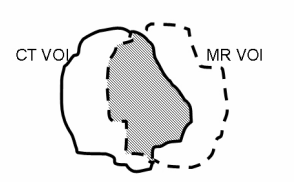

Fig. 2. Overlap between CT VOI (solid line) and MR VOI (dashed line).

OR was calculated before, after affine, and after non-linear registration steps. An OR of 100% would mean that the two VOIs are perfectly aligned.

To assess differences between microvascular parameters extracted using tracer kinetic modeling applied to the CT and MR data Bland-Altman plots [9] for K^{trans}, v_e and v_p values were employed before, after affine and after non-linear registration and using high (CT) or low (MR) resolution for parametric maps. Before registration, the comparison is between summary values calculated on the VOIs defined on each of the MR and CT datasets. After affine and non-linear registration the comparison is performed using the CT VOI for both modalities.

3. RESULTS

The graph in Fig. 3 shows the change in OR value due to the registration steps for the 5 patients.

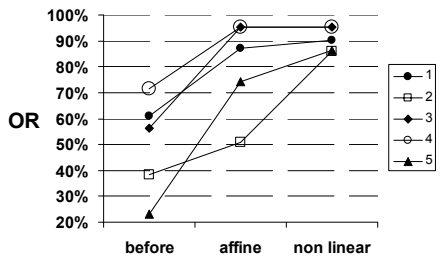

Fig. 3. OR value before, after affine, and after non-linear registration.

The use of the non-linear step after affine registration results in a percent overlap ratio of over 86 % in all cases. After affine registration the mean improvement is about 80 %, while after non-linear more than a further 18 %.

Figure 4 shows the effect of the registration steps in an individual patient, where the improvement in OR after the non-linear step is about 69 %.

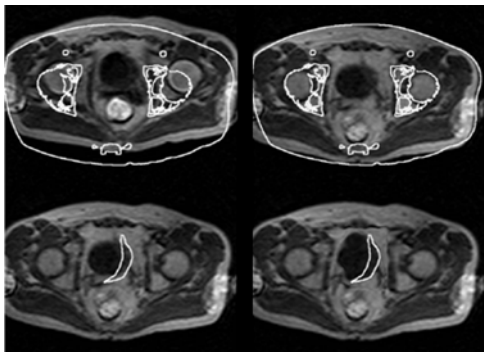

Fig. 4. Top: CT edges superimposed on MR before (left) and after affine registration (right); bottom: CT tumor VOI superimposed on MR before (left), and after non-linear registration (right). Note the deformation of the VOI to match the difference in bladder filling between the CT and MR acquisitions.

In Fig. 5 it is possible to appreciate the similarity between CT and MR parametric maps (low resolution).

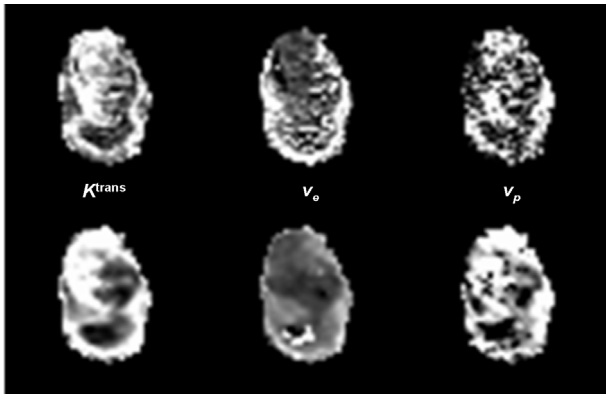

Fig. 5. An example of comparison between CT (top) and MR (bottom) parametric maps.

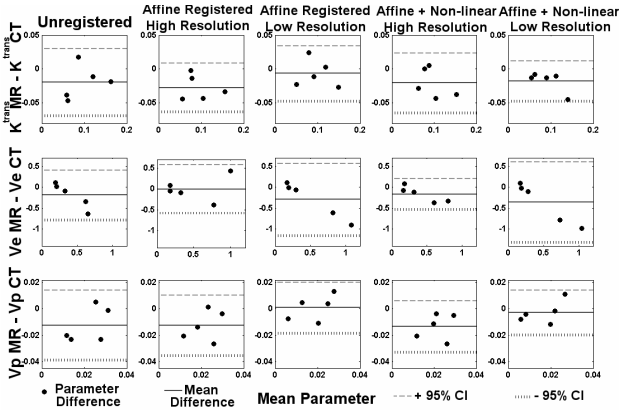

Fig.6. Bland-Altman plot comparing median K^{trans} (top), median v_e (middle) and mean v_p (bottom) in the case of non registered images (column 1), affine registered and high resolution maps (column 2), affine registered and low resolution maps (column 3), non-linear registered and high resolution maps (column 4), non-linear registered and low resolution maps (column 5).

Fig. 6 shows Bland-Altman plots for summary microvascular parameters in each patient. This figure demonstrates how the limits of agreement of the summary parameters from the two modalities are affected by registration. Non-linear registration achieves the best result for each parameter: for K^{trans} and v_p at low resolution and for v_e at high resolution.

4. DISCUSSION AND CONCLUSION

We have developed a method that allows comparison of parametric maps generated from tracer kinetic modeling between different modalities: CT and MR. The method is composed of three steps: temporal synchronization of CT and MR dynamic sets; affine registration to obtain the same spatial coordinate system for the two modalities; and a non-linear registration to correct the different shapes assumed by the tumor on the two images (acquired on different days).

To evaluate the matching of the CT and MR VOIs after registration we calculated the overlap ratio before, after affine and after non-linear registration. Our results show that in all cases the overlap ratio is better than 86 % after non-linear registration. Figure 3 illustrates the importance of the non-linear registration step. In this case the bladder and, as a consequence, the tumor had a different shape between CT and MR. The non-linear registration permitted recovery of the VOIs spatial correspondence, as demonstrated by an improvement of 69 % in overlap ratio over the affine result.

We also analyzed the degree of agreement of the summary parameters from the two modalities on comparing K^{trans}, v_e and v_p before registration, after affine registration and after non-linear registration at two resolutions (high, i.e. CT resolution and low, i.e. MR resolution). The improvements in parameter value agreement between MR and CT observed due to registration indicate that there is an improved chance of comparing corresponding tumor tissue after registration. However, we cannot expect that mean and median values are exactly the same between modalities due to the fact that scans were performed on different days. Other reasons why the parameter values may not match between modalities include the differences in the underlying mechanisms of contrast enhancement between DCE-MR and DCE-CT and differences in aspects of the scanning, including temporal resolution. Future work will involve the exploration of these possible causes of difference.

Non-linear registration achieves the best results for K^{trans} and v_p at low resolution. This could be due to reduced noise in the CT data after reducing the resolution to that of the MR data. However, for v_e the best results for non-linear registration is at high resolution. This may be due to the generally finer spatial structure observed in v_e maps.

In conclusion, this study demonstrates the feasibility of our method to facilitate the voxel-wise and summarized comparison of parameter maps obtained from DCE-MRI and DCE-CT of bladder tumors.

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